K080837

5.0 510(k) Summary

SEP 2 4 2008

As required by 21 CFR Section 807.92(c).

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Contact:	Russel K. Enns, Ph.D.
Date of Preparation:	September 19, 2008
Device:	
Trade name:	Xpert MRSA/SA SSTI Assay
Common name:	*Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) from skin and soft tissue infections Assay.
Type of Test:	Nucleic Acid Amplification Test, DNA, *Staphylococcus aureus* (SA) and Methicillin-resistant *Staphylococcus aureus* (MRSA), qualitative
Classification name:	Antimicrobial susceptibility test powder
Regulation number:	866.1640
Procode:	NQX
Classification Advisory Committee:	Microbiology
Panel:	83
Predicate Device:	Cepheid Xpert MRSA Assay [510(k) no. K070462]

Device Description:

The Cepheid Xpert MRSA/SA Skin and Soft Tissue Infection Assay (Xpert MRSA/SA SSTI Assay) is a rapid, automated DNA test for simultaneously detecting MRSA and SA directly from skin and soft tissue specimens. The specimen is collected on a double swab, which is placed in a tube containing elution reagent. Following brief vortexing, the eluted material and two single-use reagents (Reagent 1 and Reagent 2) that are provided with the assay are transferred to different, uniquely-labeled chambers of the disposable fluidic cartridge (the Xpert MRSA/SA cartridge). The user initiates a test from the system user interface and places the cartridge into the GeneXpert® Dx System instrument platform, which performs hands-off real-time, multiplex polymerase chain reaction (PCR) for detection of DNA. In this platform, additional sample preparation, amplification, and real-time detection are all fully-automated and completely integrated.

The GeneXpert® System consists of a GeneXpert instrument, personal computer, and the multi-chambered fluidic cartridges that are designed to complete sample preparation and real-time PCR for detection of MRSA and SA in approximately 50 minutes. Each system has 1 to 16 randomly accessible modules that are each capable of performing separate sample preparation and real-time PCR tests. Each module contains a syringe drive for dispensing fluids, an ultrasonic horn for lysing cells or spores, and a proprietary I-CORE® thermocycler for performing real-time PCR and detection.

The Xpert MRSA/SA Assay includes reagents for the simultaneous detection of the target organisms, SA and MRSA. The primers and probes in the Xpert MRSA/SA Assay detect nucleic acid sequences of the staphylococcal protein A (*spa*), the gene for *Mec*A-Mediated Oxacillin resistance (*mecA*), and staphylococcal cassette chromosome (SCC*mec*) inserted in the SA chromosomal *attB* site.

The test includes a sample processing control (SPC) to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR assay. The Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability.

Device Intended Use:

The Cepheid Xpert MRSA/SA Skin and Soft Tissues Infection Assay (Xpert MRSA/SA SSTI Assay) performed in the GeneXpert® Dx System is a qualitative *in vitro* diagnostic test intended for the detection of *Staphylococcus aureus* (SA) and methicillin-resistant *Staphylococcus aureus* (MRSA) from skin and soft tissue infection swabs. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA/SA DNA. The Xpert MRSA/SA SSTI Assay is indicated for use in conjunction with other laboratory tests such as microbiology culture, and clinical data available to the clinician as an aid in the detection of MRSA/SA from skin and soft tissue infections. The Xpert MRSA/SA SSTI Assay is not intended to monitor treatment for MRSA/SA infections. Concomitant cultures for SA and MRSA are necessary to recover organisms for susceptibility testing or epidemiological typing.

In a mixed culture containing MRSA/SA and other organisms (e.g. Gram negative bacilli, yeast), results can be false negative or variable depending on the concentration of MRSA/SA present, particularly if the concentration of MRSA/SA is close to the LoD of the assay.

Substantial Equivalence:

The Xpert MRSA/SA SSTI Assay is substantially equivalent to two molecular-based MRSA and SA assays, Cepheid Xpert™ MRSA Assay (K070462) and the BD GeneOhm StaphSR Assay (K071026). All three assays detect MRSA and the Xpert MRSA/SA and the BD GeneOhm StaphSR Assay detect both SA and MRSA; all three assays determine the presence of the target organisms through real-time PCR amplification and fluorogenic target-specific hybridization detection. Both Cepheid assays utilize the same fully-automated instrument system, the Cepheid GeneXpert Dx System.

The Xpert MRSA/SA SSTI Assay simultaneously detects SA and MRSA from skin and soft tissue specimens. The Xpert MRSA Assay detects MRSA from nasal swab specimens. The BD GeneOhm StaphSR Assay detects SA and MRSA from positive blood cultures. Table 5.1 shows the similarities and differences between the Xpert MRSA/SA SSTI Assay and the two molecular-based predicate devices.

The Xpert MRSA/SA SSTI is also substantially equivalent to conventional microbiology-based predicate devices that identify (ID) and/or test for antimicrobial susceptibility (AST) of gram positive organisms, including Staphylococcus species of human origin from pure culture isolates. These conventional microbiology-based predicates accommodate multiple specimen types, including swabbed specimens of skin and soft tissue infections. These conventional microbiology-based predicates are:

- Remel Staphaurex Latex Agglutination Test (K851949),
- BBL (BD) Oxacillin Screen Agar (K863821),
- BD BBL CHROMagar MRSA (K042812
- BD Phoenix Automated Microbiology ID/AST System (K020322 and K023301).

Table 5.2 compares the new device with the conventional microbiology-based assays for SA. Table 5.3 compares the new device with the conventional microbiology-based assays for MRSA.

A multi-center study was conducted on 848 patients to determine the performance characteristics of the device relative to the sensitivity and specificity of culture and susceptibility testing, the current standard of care. The test results showed the Xpert MRSA/SA SSTI to be substantially equivalent to the current standard of care, identification of *Staphyloccoccus aureus* from solid media by catalase, coagulase, and Gram stain, and susceptibility by cefoxitin disk diffusion test.

Table 5.1

Similarities and Differences Between the Xpert MRSA/SA SSTI Assay and the Molecular-based Predicate Devices

Similarities			
	Device	**Predicates**	
Item	**Xpert MRSA/SA SSTI Assay**	**Xpert MRSA Assay (K070462)**	**BD GeneOhm™ StaphSR Assay (K071026)**
Intended Use	Rapid detection of MRSA and SA	MRSA only	Same
Indication for Use	Identification of MRSA and SA	MRSA only	Same
Technological Principles	Fully-automated nucleic acid amplification (DNA); real-time PCR	Same	Same
Test Cartridge	Disposable single-use, multi-chambered fluidic cartridge.	Same	Disposable single-use PCR tube
Instrument System	Cepheid GeneXpert Dx System	Same	Cepheid SmartCycler
Fluidics	Self-contained and automated after swab elution and two single-dose reagent additions.	Same	Manual
Probes	TaqMan® Probes	Same	Molecular Beacons
Internal Controls	Sample processing control (SPC) and probe check control (PCC).	Same	One internal reagent control and external positive and negative controls required per run
DNA Target Sequence	Sequence incorporating the insertion site (*attBssc*) of Staphylococcal Cassette Chromosome *mec* (SCC*mec*) for detection of MRSA.	Same	Same
	Sequence specific to methicillin/oxacillin resistance (*mecA* gene)	N/A	N/A
Rapid test results	Approximately 50 minutes to results.	Approximately 75 minutes to results.	Approximately 60-75 minutes.

Similarities			
	Device	**Predicates**	
Item	**Xpert MRSA/SA SSTI Assay**	**Xpert MRSA Assay (K070462)**	**BD GeneOhm™ StaphSR Assay (K071026)**
Users	Operators with no clinical lab experience to experienced clinical laboratory technologists.	Same. Categorized as a CLIA moderate complexity assay.	CLIA High Complexity Laboratory Users

Differences			
Item	**Device**	**Predicates**	
	Xpert MRSA/SA SSTI Assay	**Xpert MRSA Assay (K070462)**	**BD GeneOhm™ StaphSR Assay (K071026)**
Intended Use	Simultaneous rapid detection of SA and MRSA.	Only detects MRSA.	Same
Specimen Type	Direct from skin and soft tissue infection swabs.	Direct from nasal swabs.	Direct from Positive Blood Cultures
DNA Target Sequence	Sequence specific to *Staphylococcus aureus* species (*spa* gene)	N/A	Sequence specific to *Staphylococcus aureus* species (*nuc* gene)
Ability to identify correctly "Empty Cassette Variants"	Yes, sequence specific to *Staphylococcus aureus* species (*mecA* gene)	No	No

Table 5.2

Similarities and Differences Between the Xpert MRSA/SA SSTI Assay and the Conventional Microbiology-based Predicate Devices for *Staphylococcus aureus* (SA) only

Similarities		
Item	**Device**	**Predicates (SA only)**

	Xpert MRSA/SA SSTI Assay	Staphaurex Latex Agglutination Test for SA K851949	BD Phoenix Automated Microbiology System for SA K020322
Intended Use	Detection of SA	Same	Same
Single use	Yes	Same	Same
Assay Controls	Positive Control: SA Negative Control: *S. epidermidis*	Same	Same

Differences			
Item	**Device**	**Predicates (SA only)**	
	Xpert MRSA/SA SSTI Assay	**Staphaurex Latex Agglutination Test for SA K851949**	**BD Phoenix Automated Microbiology System for SA K020322**
Mode of Detection	Sequence specific to *Staphylococcus aureus* species (*spa* gene)	Clumping factor and protein A	Microbial utilization and degradation of specific substrates
Specimen Type	Direct from skin and soft tissue infection swabs.	Staphylococcus species	Gram Positive organisms
Assay format	Amplification: PCR Detection: Fluorogenic target-specific hybridization	Agglutination with latex particles sensitized with fibrinogen and IgG	Conventional, chromogenic and fluorogenic biochemical tests for identification (ID) and antimicrobial resistance test (AST)
Interpretation of test results	Diagnostic software of the GeneXpert Dx System	Visual interpretation	Automated

Table 5.3

Similarities and Differences Between the Xpert MRSA/SA SSTI Assay and the Conventional Microbiology-based Predicate Devices for Methicillin-Resistant *Staphylococcus aureus* (MRSA)

Similarities				
Item	**Device**	**Predicates (MRSA only)**		
	Xpert MRSA/SA SSTI Assay	**Mueller Hinton Agar w/ 4% NaCl and Oxacillin (Oxacillin Screen Agar Test) K863821**	**BBL CHROMagar MRSA (K042812)**	**BD Phoenix Automated Microbiology System K023301**
Intended Use	Detection of MRSA	Same	Same	Same
Single use	Yes	Same	Same	Same
Assay Controls	Positive Control: MRSA Negative Control: SA	Same	Same	Same

Differences				
Item	**Device**	**Predicates (MRSA only)**		
	Xpert MRSA/SA SSTI Assay	**Mueller Hinton Agar w/ 4% NaCl and Oxacillin (Oxacillin Screen Agar Test) K863821**	**BBL CHROMagar MRSA (K042812)**	**BD Phoenix Automated Microbiology System K023301**

Differences				
Item	**Device**	**Predicates (MRSA only)**		
	Xpert MRSA/SA SSTI Assay	**Mueller Hinton Agar w/ 4% NaCl and Oxacillin (Oxacillin Screen Agar Test) K863821**	**BBL CHROMagar MRSA (K042812)**	**BD Phoenix Automated Microbiology System K023301**
Mode of Detection for methicillin resistance	SCC*mec* gene specific for MRSA *mecA* gene specific for methicillin/ oxacillin resistance	Growth on Mueller Hinton Agar with 4% NaCl and 6 ug/ml oxacillin	Use of specific Chromogenic substrates and cefoxitin to differentiate MRSA from other organisms	Utilizes a redox indicator for detection of organism growth in the presence of an antimicrobial agent
Specimen Type	Direct from skin and soft tissue infection swabs.	Pure culture isolate of *Staphylococcus aureus*	Direct from Anterior nares	Pure culture isolate of *Staphylococcus aureus*
Assay format	Amplification: PCR Detection: Fluorogenic target-specific hybridization	Phenotypic detection based on a 24 hour growth of SA inoculated on media	Phenotypic detection base on a 24-48 hour growth of SA (mauve colonies) inoculated on media	AST panels containing MIC tests for several antimicrobial agents
Interpretation of test results	Diagnostic software of the GeneXpert Dx System	Manual: Visual interpretation	Manual: Visual interpretation	Automated

Non-Clinical Studies:

Analytical Inclusivity Study on CDC *Staphylococcus aureus* Specimens

The analytical inclusivity of the Xpert MRSA/SA Assay was determined using Staphylococcus *aureus* strains that were reported by the Center for Disease Control

(CDC) to be representative of MRSA and MSSA strains currently encountered in the healthcare community. All strains were tested in triplicate using 100 µL of stationary phase cell suspensions diluted 10 million-fold. The panel consisted of MRSA strains representing SCC*mec* types II, IV, IVa, IVb, and IVc in addition to several unknown types. Data supplied by the Center for Disease Control (CDC) indicated these strains, when characterized by pulsed-field gel electrophoresis (PFGE), represent numerous USA types including USA100, the most common hospital-acquired strain and USA300 and USA400, the most common community-acquired strains.[1]

All 21 MRSA strains were correctly reported MRSA positive; SA positive using the Xpert MRSA/SA Assay. Additionally, each MSSA strain (n=3) was correctly reported MRSA negative; SA positive. Culture using BBL CHROMagar MRSA confirmed all Xpert test results. Colony forming units per assay were determined by plate counts in duplicate.

Analytical Inclusivity Study on Expanded Panel of *Staphylococcus aureus* Specimens

One hundred twenty-one (121) additional *Staphylococcus aureus* strains were tested using the Xpert MRSA/SA Assay. Overnight cultures were grown in Brain Heart Infusion (BHI) broth and adjusted to 0.5 McFarland units. All strains were tested in triplicate using 100 µL of cultures further diluted 100 thousand to one million-fold.

MRSA (78) and SA (43) strains were selected to broadly represent the range of genetic diversity found in the species *Staphylococcus aureus* based on phylogenetic structure. Selections represent primary lineages with emphasis on specific clonal complexes within which MRSA is predominantly observed. Lineages that contain MRSA and SA, as well as those that contain SA exclusively were included.

The Xpert MRSA/SA Assay correctly identified 116 of 121 strains. The 5 discordants were characterized by catalase, tube coagulase, and Gram stain. *Mec*A-Mediated Oxacillin resistance was assessed by disk diffusion using a 30 µg cefoxitin disk and a diameter cut-off of 21/22 mm.

Three (3) of 78 MRSA strains were reported MRSA negative; SA positive using the Xpert assay. Further characterization indicates these strains are not resistant and were correctly reported MRSA negative; SA positive.

Two (2) of 43 SA strains were reported MRSA positive; SA positive using the Xpert assay. Further characterization indicates these strains are resistant and were correctly reported MRSA negative; SA positive.

Each of the 12 known USA300 isolates were correctly reported MRSA positive and SA positive as expected.

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[1] McDougal L, Steward C, Killgore G, Chaitram J, McAllister S, Tenover F. Pulsed-Field Gel Electrophoresis Typing of Oxacillin-Resistant *Staphylococcus aureus* Isolates from the United States: Establishing a national Database. J Clin Micro 2003;41(11):5113-20.

Evaluation of Empty Cassette Variants

Twenty-two (22) *Staphylococcus aureus* isolates identified as "empty cassette variants" were tested using the Xpert MRSA/SA Assay. Overnight cultures were adjusted to 0.5 McFarland units. All strains were tested from cultures further diluted 100-fold (high) and 100 thousand-fold (low).

The Xpert MRSA/SA Assay correctly identified all 22 isolates as MRSA negative and SA positive. At both cell concentrations tested, only Cts for the *spa* and SCC*mec* targets were reported. No *mecA* Cts were reported

Analytical Sensitivity

Limit of Detection Studies

Studies were performed to determine the 95% confidence intervals for the analytical limit of detection (LoD) of *Staphylococcus aureus* (SA) cells and methicillin-resistant *Staphylococcus aureus* (MRSA) cells diluted into a surrogate wound matrix of human origin. The surrogate wound matrix consisted of a white blood cell (WBC) concentrate prepared from whole blood by centrifugation. The matrix also contained red blood cells (RBC) and plasma, and a negligible amount of anticoagulant (CPD or CPDA-1). The limit of detection is defined as the lowest number of colony forming units (CFU) per sample that can be reproducibly distinguished from negative samples with 95% confidence or the lowest concentration at which 19 of 20 replicates were positive.

For MRSA, replicates of 20 were evaluated at each MRSA concentration tested (CFU/swab) for 6 individual isolates representing SCC*mec* types I, II, III, IVa, V, and VI. When characterized by pulsed-field gel electrophoresis (PFGE), USA100, the most common healthcare-acquired strain and USA400, one of the most common community-acquired strains were represented.

For SA, replicates of 20 were evaluated at each SA concentration (CFU/swab) for 3 individual SA isolates. USA types USA900 and USA1200 were represented.

The estimate and confidence intervals were determined using logistic regression with data (number of positive results per number of replicates at each level) over the range of CFU/swab tested. The confidence intervals were determined using maximum likelihood estimates on the logistic model parameters using the large sample variance-covariance matrix. The LoD point estimates and 95% upper and lower confidence intervals for each SA and each MRSA SCC*mec* type tested are summarized in Tables 5.4 and 5.5.

Table 5.4: LoD and Confidence Intervals - SA

SA Strain ID	PFGE	LoD (CFU/swab)	Lower 95% CI	Upper 95% CI
N7129	USA900	51	42	69

102-04	USA1200	87	76	109
29213	unknown	123	97	188

Table 5.5: LoD and Confidence Intervals - MRSA

MRSA Strain ID	SCC*mec* Type	PFGE	LoD (CFU/swab)	Lower 95% CI	Upper 95% CI
64/4176	I	USA500	221	195	271
N315	II	USA100	122	106	152
11373	III	unknown	124	115	155
MW2	IVa	USA400	82	68	113
ST59-MRSA-V	V	USA1000	242	208	305
HDE288	VI	USA800	183	161	223
64/4176	I	USA500	221	195	271

The results of this study indicate that the Xpert MRSA/SA SSTI Assay will produce a positive SA result 95% of the time with 95% confidence for a wound swab containing 123 CFU and a positive MRSA result 95% of the time with 95% confidence for a wound swab containing 300 CFU.

Linearity

A study was conducted to define the reportable range of the Xpert MRSA/SA Assay and demonstrate a linear relationship between SA and MRSA input and assay output (Ct). Linearity was evaluated using ten-fold serial dilutions (1e8 CFU/sample – 10 CFU/sample) of SA and MRSA isolates.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.998$) with respect to *spa* detection as a function of SA cell input over 6 logs. The mean reportable Ct range = 13.4 to 33.1. PCR efficiency for the *spa* reaction is 100%.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.999$) with respect to *spa* detection as a function of MRSA cell input over 6 logs. The mean reportable Ct range = 14.3 to 35.0. PCR efficiency for the *spa* reaction is 95.4%.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.999$) with respect to *mecA* detection as a function of MRSA cell input over 6 logs. The mean reportable Ct range = 14.2 to 35.3. PCR efficiency for the *mecA* reaction is 93.3%.

The Xpert MRSA/SA Assay responds linearly ($r^2 = 0.999$) with respect to SCC*mec* detection as a function of MRSA cell input over 5 logs. The mean reportable Ct range for SCC*mec* is 16.6 to 33.8. PCR efficiency for the *mec* reaction is 94.6%

Analytical Specificity

Cross-reactivity Study

One hundred five (105) strains were collected, quantitated and tested using the Xpert MRSA/SA Assay. The 98 cultures from the American Type Culture Collection (ATCC) and 7 strains from the Network on Antimicrobial Resistance in *Staphylococcus aureus* (NARSA) represent species phylogenetically related to *Staphylococcus aureus* or those potentially encountered in a hospital environment.

Of these, methicillin-sensitive coagulase negative staphylococci (29) and methicillin-resistant coagulase negative staphylococci (9) were included. The organisms tested were identified as either Gram positive (74), Gram negative (28), or yeast (3). The organisms were further classified as either aerobic (95) or anaerobic (10).

Two (2) or more replicates of each isolate were tested at 1.7 - 3.2 McFarland units. Under the conditions of the study, all isolates were reported MRSA negative and SA negative; none of the isolates were detected by the Xpert MRSA/SA Assay. Positive and Negative controls were included in the study. The analytical specificity was 100%.

Evaluation of BORSA Strains

Seven (7) well characterized borderline oxacillin-resistant *Staphylococcus aureus* (BORSA) strains were tested, including one apparent "empty cassette" (see above). Methicillin-resistant *Staphylococcus aureus* is resistant to all ß-lactam drugs through the alternative penicillin-binding protein PBP2a encoded by *mecA*[15]. BORSA strains are *mecA* negative, but exhibit an oxacillin minimum inhibitory concentration (MIC) ≥ 2 and ≤ 8 µg/mL. It is especially valuable to distinguish MRSA from BORSA to prevent the unnecessary and inappropriate use of vancomycin and isolation precautions not warranted for patients infected with a ß-lactam susceptible strain[16].
Under the conditions of this study, all 7 BORSA isolates (including the apparent "empty cassette" isolate) were reported MRSA negative; SA positive at both high and low cell concentrations using the Xpert MRSA/SA Assay. No *mecA* signals were reported. These results demonstrate that a BORSA strain will be correctly identified as MRSA negative; SA positive and will not report a false positive MRSA test result using the Xpert MRSA/SA Assay.

Interfering Substances

In the investigational study for Xpert MRSA/SA SSTI Assay, 428 of the 848 specimens were observed to contain blood, and 404 were observed to contain other non-specific substances, which could potentially interfere with the assay (note that some specimens contained more than one type of potential contaminant). Fisher's exact tests conducted on the data generated from swabs with and without these potential interfering substances demonstrated that their presence did not affect the assay performance.

In a non-clinical study, potentially interfering substances that may be present in clinical skin and soft tissue infection specimens were evaluated directly relative to the performance of the Xpert MRSA/SA Assay. Potentially interfering substances in skin and soft tissue infections may include, but are not limited to: blood, pus, plasma, topical ointments (antibiotic/antiseptic/pain relieving), debriding agents, and tinctures. These substances are listed in Table 5.6a and Table 5.6b with the active ingredients and concentrations tested shown. Inhibition of the MRSA/SA assay has been observed with the following substances: StaphA + Septic (5% w/v), Hydrocortisone (5% w/v), and antibacterial hand sanitizer (5% w/v).

Table 5.6a: Potentially Interfering SSTI Substances Tested

Substance	Active Ingredient	% Tested
TET Buffer (control)	Control	Control
Buffy Coat (wound stimulant)	WBC (1.5e9/mL)	50% (v/v)
Whole Blood (MRSA/SA free)	N/A	50% (v/v)
Plasma		50% (v/v)
Neosporin	400 units Bacitracin 5,000 units Polymyxin B 3.5 mg Neomycin	1% and 5% (w/v)
StaphA^{+}Septic	0.2% Benzethonium Chloride, 2.5% Lidocaine HCl	1% and 5% (w/v)
Hyrdocortisone	1% Hyrdocortisone	1% and 5% (w/v)
Biol-Ease	20% Benzocaine	1% and 5% (w/v)
Iodine Tincture	2% Iodine	50% (v/v)

Table 5.6b: Potential Interfering SSTI Substances Tested

Substance	Active Ingredient	% Tested
TET Buffer (control)	Control	Control
Mupirocin	0.2% Benzethonium Chloride 2.5% Lidocaine HCl	5% (w/v)
Saline	0.65% Sodium Chloride	50% (v/v)
Antibacterial hand sanitizer	62% Ethyl alcohol	1% (w/v)

Antibacterial hand sanitizer	62% Ethyl alcohol	5% (w/v)
70% Isopropyl alcohol	70% Isopropyl alcohol	50% (v/v)

Clinical Studies

Performance Characteristics

Clinical Performance

Performance characteristics of the Xpert MRSA/SA SSTI Assay were determined in a multi-site prospective investigation study at four US institutions by comparing the Xpert MRSA/SA SSTI Assay with reference culture. Subjects included individuals whose routine care called for collection of a swab from the patient's skin and soft tissue infection for culture.
Double swabs were collected from each subject. One swab was tested by the Xpert MRSA/SA SSTI Assay at the enrolling center and the other swab was tested by the site's standard method, and the remaining specimen was sent to the central laboratory for reference culture testing.

At the centralized laboratory, the specimen was enriched overnight in trypticase soy broth with 6.5% NaCl. The trypticase soy broth was then streaked onto plates with cefoxitin (for MRSA) and without cefoxitin (for SA). If either or both the SA or MRSA plates showed *S. aureus* presumptive colonies, the colonies were sub-cultured onto a blood agar plate. Confirmation of presumptive positive colonies was performed with catalase, tube coagulase, and Gram stain. *Mec*A-Mediated Oxacillin resistance was tested by disk diffusion test using a 30 μg cefoxitin disk and cutoff of 21/22 mm. If the cultures for both the SA and MRSA plates were determined to be negative, the archived trypticase soy broth with 6.5% NaCl was subcultured onto blood agar followed by workup for SA/MRSA as previously described.

Performance of the Xpert MRSA/SA SSTI Assay was calculated relative to the reference culture results.

Overall Results

A total of 848 specimens were tested for MRSA and SA by Xpert MRSA/SA SSTI Assay and culture.

Among the 848 cases in the eligible dataset, antibiotic use within the 3 weeks prior to sample collection was reported for 207 subjects, and no antibiotic use was confirmed for 441 subjects; for 200 cases, antibiotic status was unknown. A statistically significant decrease in the positivity rate of SA with respect to culture results was observed when antibiotics were used (p=0.007); this phenomenon has also been reported in the literature.[10-14] The MRSA positivity rate for culture was also decreased, although to a lesser extent (p=0.022). The decrease in positivity was not observed with the Xpert MRSA/SA Assay when antibiotics were used nor was any inhibition observed in the assay in the presence of topical antibiotics (see Interfering Substances). The decreased culture positivity rates for MRSA and SA in the presence of antibiotics caused the higher than expected false positive rates observed with the Xpert MRSA/SA SSTI Assay.

Five (5) of the 246 MRSA positive cultures had mixed infections of MRSA and SA. Xpert MRSA/SA SSTI identified 3 of the 5 mixed infections as MRSA positive and 2 of the five as SA positive/MRSA negative.

The performance of the Xpert MRSA/SA SSTI Culture Assay is summarized in Tables 5.7a-5.7c.

Table 5.7a: MRSA/SA Performance in Subjects with No Antibiotic Use (within 3 weeks of sample collection) vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	137[a]	2	6	145
	SA+/MRSA-	3[b]	79	16	98
	SA-	6	4	188	198
	Total	146	85	210	441

[a]1 of the 137 were mixed infections of MRSA and SA.
[b]2 of the 3 were mixed infections of MRSA and SA.

Positive Percent Agreement (MRSA+) = 93.8%; 95%Confidence Interval = 88.6-97.1
Negative Percent Agreement (MRSA+) = 97.3%; 95%Confidence Interval = 94.7-98.8
Positive Percent Agreement (SA+/MRSA+) = 95.7%; 95%Confidence Interval = 92.2-97.9
Negative Percent Agreement (SA+/MRSA+) = 89.5%; 95%Confidence Interval = 84.6-93.3

Among subjects with no antibiotic use within the 3 weeks prior to sample collection, the Xpert MRSA/SA SSTI Assay identified 93.8% of the specimens positive for MRSA and 97.3% of the specimens negative for MRSA relative to the reference culture method, and

95.7% of the specimens positive for SA and 89.5% of the specimens negative for SA relative to the reference culture method.
Among these subjects with no antibiotic use, 96.8% (427/441) were successful on the first attempt with the Xpert MRSA/SA Assay. The remaining 14 gave indeterminate results on the first attempt (6 "INVALID", 7 "ERROR" and 1 "NO RESULT"). Of the 14 indeterminate on the first attempt, all gave a result on the second attempt.

Table 5.7b: MRSA/SA Performance in Subjects with Unknown Antibiotic Use (within 3 weeks of sample collection) vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	47[c]	0	4	51
	SA+/MRSA-	2	45	8	55
	SA-	1	2	91	94
	Total	50	47	103	200

[c]2 of the 47 were mixed infections of MRSA and SA.
Positive Percent Agreement (MRSA+) = 94.0%; 95%Confidence Interval = 83.5-98.7
Negative Percent Agreement (MRSA+) = 97.3%; 95%Confidence Interval = 93.3-99.3
Positive Percent Agreement (SA+/MRSA+) = 96.9%; 95%Confidence Interval = 91.2-99.4
Negative Percent Agreement (SA+/MRSA+) = 88.3%; 95%Confidence Interval = 80.5-93.8

When it was unknown if subjects took antibiotics within the 3 weeks prior to sample collection, the Xpert MRSA/SA SSTI Assay identified 94.0% of the specimens positive for MRSA and 97.3% of the specimens negative for MRSA relative to the reference culture method, and 96.9% of the specimens positive for SA and 88.3% of the specimens negative for SA relative to the reference culture method.
Among these subjects with unknown antibiotic use, 97.0% (194/200) were successful on the first attempt with the Xpert MRSA/SA Assay. The remaining 6 gave indeterminate results on the first attempt (2 "INVALID", 3 "ERROR" and 1 "NO RESULT"). Of the 6 indeterminate on the first attempt, all gave a result on the second attempt.

Table 5.7c: MRSA/SA Performance in Subjects with Known Antibiotic Use (within 3 weeks of sample collection) vs. Reference Culture

		Culture			
		MRSA+	SA+/MRSA-	Neg/No Growth	Total
Xpert	MRSA+	44	2	10	56
	SA+/MRSA-	3	31	19	53
	SA-	3	1	94	98
	Total	50	34	123	207

Positive Percent Agreement (MRSA+) = 88.0%; 95%Confidence Interval = 75.7-95.5

Negative Percent Agreement (MRSA+) = 92.4%; 95%Confidence Interval = 87.0-96.0
Positive Percent Agreement (SA+/MRSA+) = 95.2%; 95%Confidence Interval = 88.3-98.7
Negative Percent Agreement (SA+/MRSA+) = 76.4%; 95%Confidence Interval = 67.9-83.6

Among subjects with known antibiotic use within the 3 weeks prior to sample collection, the Xpert MRSA/SA SSTI Assay identified 88.0% of the specimens positive for MRSA and 92.4% of the specimens negative for MRSA relative to the reference culture method, and 95.2% of the specimens positive for SA and 76.4% of the specimens negative for SA relative to the reference culture method.
Among these subjects with antibiotic use, 96.1% (199/207) of these eligible specimens were successful on the first attempt with the Xpert MRSA/SA Assay. The remaining 8 gave indeterminate results on the first attempt (5 "INVALID" and 3 "ERROR"). Of the 8 indeterminate on the first attempt, all gave a result on the second attempt.

Empty Cassette Variants

For an isolate to be identified as MRSA positive with the Xpert MRSA/SA SSTI Assay, the test for *spa* must be positive as well as the test for *mecA* and SCC*mec*. An isolate that is positive for *spa* and SCC*mec*, but not *mecA* is reported SA because it is methicillin-sensitive. This situation can occur when the portion of the SCC*mec* element carrying *mecA* is excised, but the ends of this mobile element remain in place, yielding a positive SCC*mec* signal. These isolates are sometimes referred to as "empty cassette variants" and are not uncommon in the clinical environment. The significance of these isolates is to potentially confound an assay for MRSA that does not detect the *mecA* gene directly. The Xpert MRSA/SA Assay was designed to correctly identify these variants as SA.

Among the eligible specimens included in the data analyses presented in this report, a total of 16 isolates fit the empty cassette profile resulting in positive *spa* and SCC*mec* test results, but no *mecA* detection (Ct = 0) as shown in Table 5.8. Fifteen of the 16 were verified MRSA true negative isolates relative to culture, and 14 of 16 were verified true positive SA isolates relative to culture. One isolate was identified as MRSA by culture and 2 isolates were both MRSA and SA negative by culture.

Table 5.8 : MRSA/SA SSTI Performance vs. Reference Culture – Empty Cassette Variants

Subject #	Xpert Result	*spa* (Ct)	*mecA* (Ct)	SCC*mec* (Ct)	Culture	Xpert v. Culture	
						MRSA	SA
1	SA	23.6	0	26.0	SA	TN	TP
2	SA	14.7	0	16.5	SA	TN	TP
3	SA	20.5	0	34.0	SA	TN	TP
4	SA	18.4	0	21.0	SA	TN	TP
5	SA	15.6	0	28.4	MRSA	FN	TP
6	SA	17.2	0	31.6	SA	TN	TP
7	SA	34.1	0	35.6	Neg	TN	FP
8	SA	29.1	0	33.0	SA	TN	TP
9	SA	12.7	0	23.5	SA	TN	TP
10	SA	18.2	0	27.6	SA	TN	TP
11	SA	18.4	0	22.0	SA	TN	TP
12	SA	25.5	0	27.7	SA	TN	TP
13	SA	20.0	0	22.1	Neg	TN	FP
14	SA	26.0	0	28.3	SA	TN	TP
15	SA	23.9	0	25.7	SA	TN	TP
16	SA	19.9	0	34.0	SA	TN	TP

Carry-Over Contamination Study

A study was conducted to demonstrate that single-use, self-contained GeneXpert cartridges prevent carry-over contamination in negative samples run following very high positive samples in the same GeneXpert module. The study consisted of a negative sample processed in the same GeneXpert module immediately following a very high MRSA positive sample (roughly 10^7 CFU/test). This was repeated 20 times between 2 GeneXpert modules for a total of 42 runs. There was no evidence of any carry-over contamination. All 21 positive samples were correctly reported MRSA positive: SA positive. All 21 negative samples were correctly reported MRSA negative; SA negative.

Reproducibility Study

A panel of 10 specimens with varying concentrations of SA, MRSA and *Staphylococcus epidermidis* (negative) were tested in duplicate on 10 different days at each of the three sites (10 specimens x 2 times/ day x 10 days x 3 sites). One lot of Xpert MRSA/SA kit was used at each of the 3 testing sites. Xpert MRSA/SA assays were performed according to the Xpert MRSA/SA procedure.

Table 5.9 – Summary of Reproducibility Results

Specimen ID	Site 1	Site 2	Site 3	% Total Agreement
Neg (MSSE)	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA High Neg	100% (20/20)	100% (20/20)	90% (18/20)	96.7% (58/60)
SA Low Pos[1]	90% (18/20)	95% (19/20)	75% (15/20)	86.6% (52/60)
SA Moderate Pos[2]	100% (20/20)	100% (20/20)	95% (19/20)	98.3% (59/60)
MRSA1 High Neg	100% (20/20)	90% (18/20)	100% (20/20)	96.6% (58/60)
MRSA1 Low Pos[1]	85% (17/20)	70% (14/20)	65% (13/20))	73.3% (44/60)
MRSA1 Moderate Pos[2]	100% (20/20)	100% (20/20)	95% (18/20)	96.6% (58/60)
MRSA2 High Neg	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 Low Pos[1]	100% (20/20)	100% (20/20)	95% (19/20)	98.3% (59/60)
MRSA2 Moderate Pos[2]	100% (20/20)	95% (19/20)	95% (19/20)	96.6% (58/60)
% Total Agreement by Site	97.5% (195/200)	95% (190/200)	90% (180/200)	94.2% (565/600)

Table 5.10 – Summary of Ct Value Results by Sample Level and Probe

SPC			
Level	Mean	Std Dev	%CV
MRSA1 High Neg	34.52	0.82	2.36
MRSA2 High Neg	34.46	0.85	2.46
Neg (MSSE)	34.44	0.90	2.62
SA High Neg	34.38	0.92	2.66

Spa			
Level	Mean	Std Dev	%CV
MRSA1 Low Pos	32.96	0.8	2.44
MRSA2 Low Pos	31.05	0.69	2.21
SA Low Pos	33.91	0.8	2.35

mecA			
Level	Mean	Std Dev	%CV
MRSA1 Low Pos	33.25	0.80	2.40
MRSA2 Low Pos	31.50	0.68	2.16

SCC*mec*			
Level	Mean	Std Dev	%CV
MRSA1 Low Pos	34.19	0.90	2.63
MRSA2 Low Pos	33.13	0.68	2.05

A second reproducibility study was performed using a panel of 4 specimens of (SA: 10X LoD, MRSA1: 10X LoD, MRSA2: 10X LoD, and Negative Control: *Staphylococcus epidermidis*). The panels were tested in duplicate on 10 different days at each of the three sites (4 specimens x 2 times/ day x 10 days x 3 sites). One lot of Xpert MRSA/SA SSTI Assay was used at each of the 3 testing sites. Xpert MRSA/SA assays were performed according to the Xpert MRSA/SA procedure. The correct results were obtained in 239 of 240 tests.

Table 5.11 – Summary of Second Reproducibility Results

Specimen ID	Site 1	Site 2	Site 3	Total Agreement
Neg (MSSE)	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
SA Moderate Pos[1]	100%	100%	100%	100%

	(20/20)	(20/20)	(20/20)	(60/60)
MRSA1 Moderate Pos[1]	100% (20/20)	100% (20/20)	100% (20/20)	100% (60/60)
MRSA2 Moderate Pos[1]	100% (20/20)	100% (20/20)	95% (19/20)	98.3% (59/60)
% Total Agreement by Site	100% (80/80)	100% (80/80)	98.8% (79/80)	99.6% (239/240)

[1]10X LoD

Table 5.12 – Summary of Ct Value Results by Sample Level and Probe

SPC			
Level	Mean	Std Dev	%CV
MRSA1 Moderate Pos	35.72	1.87	5.24
MRSA2 Moderate Pos	36.29	2.66	7.34
SA Moderate Pos	34.55	1.19	3.44
NEG	34.45	1.06	3.09

Spa			
Level	Mean	Std Dev	%CV
MRSA1 Moderate Pos	29.52	1.30	4.40
MRSA2 Moderate Pos	28.91	1.03	3.57
SA Moderate Pos	30.59	0.91	2.99

mecA			
Level	Mean	Std Dev	%CV
MRSA1 Moderate Pos	29.78	1.28	4.29
MRSA2 Moderate Pos	29.32	1.24	4.22

SCC*mec*			
Level	Mean	Std Dev	%CV
MRSA1 Moderate Pos	31.49	1.26	3.99
MRSA2 Moderate Pos	31.05	1.12	3.59

Conclusions

The results of the nonclinical analytical and clinical performance studies summarized above demonstrate that the MRSA/ST SSTI Assay is as safe, as effective, and performs as well as or better than the predicate device.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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SEP 2 4 2008

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Re: k080837
Trade/Device Name: Xpert™ MRSA/SA SSTI Assay
Regulation Number: 21 CFR 866.1640
Regulation Name: Antimicrobial Susceptibility Test Powder
Regulatory Class: Class II
Product Code: NQX
Dated: August 1, 2008
Received: August 4, 2008

Dear Dr. Enns:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801), please contact the Office of In Vitro Diagnostic Device Evaluation and Safety at 240-276-0450. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). For questions regarding postmarket surveillance, please contact CDRH's Office of Surveillance and Biometric's (OSB's) Division of Postmarket Surveillance at 240-276-3474. For questions regarding the reporting of device adverse events (Medical Device Reporting (MDR)), please contact the Division of Surveillance Systems at 240-276-3464. You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (240) 276-3150 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html.

Sincerely yours,

Sally A. Hojvat, M.Sc., Ph.D.
Director
Division of Microbiology Devices
Office of *In Vitro* Diagnostic Device
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Radiological Health

Enclosure

4.0 Indications for Use Statement

510(k) Number (if known): k080837

Device Name: Xpert MRSA/SA SSTI

Indications for Use:

The Cepheid Xpert MRSA/SA Skin and Soft Tissues Infection Assay (Xpert MRSA/SA SSTI Assay) performed in the GeneXpert® Dx System is a qualitative in vitro diagnostic test intended for the detection of Staphylococcus aureus (SA) and methicillin-resistant Staphylococcus aureus (MRSA) from skin and soft tissue infection swabs. The test utilizes automated real-time polymerase chain reaction (PCR) to detect MRSA/SA DNA. The Xpert MRSA/SA SSTI Assay is indicated for use in conjunction with other laboratory tests such as microbiology culture, and clinical data available to the clinician as an aid in the detection of MRSA/SA from skin and soft tissue infections. The Xpert MRSA/SA SSTI Assay is not intended to monitor treatment for MRSA/SA infections. Concomitant cultures for SA and MRSA are necessary to recover organisms for susceptibility testing or epidemiological typing. In a mixed culture containing MRSA/SA and other organisms (e.g. Gram negative bacilli, yeast), results can be false negative or variable depending on the concentration of MRSA/SA present, particularly if the concentration of MRSA/SA is close to the LoD of the assay.

Prescription Use ___X____ (Part 21 CFR 801 Subpart D) AND/OR Over-The-Counter Use _____ (21 CFR 801 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE OF NEEDED)

Division Sign-Off

Office of In Vitro Diagnostic Device Evaluation and Safety

510(k) K080837